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(54) Title: BLOCK COPOLYMER (57) Abstract The present invention provides a block copolymer capable of retaining drugs, there being chemical cross-linking between the soft segments, such block copolymers providing improved cohesion and drug storage capacity. Transdermal patches having such copolymers, especially as adhesives, are also provided.		

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BLOCK COPOLYMER

The present invention relates to block copolymers useful in transdermal patches as adhesives and/or drug retention means, as well as to transdermal patches comprising such block copolymers.

Transdermal patches are well known in the pharmaceutical industry and are used to deliver drugs into the skin of a patient. Drug delivery by use of a transdermal patch has a number of advantages over oral delivery methods. For example, the drug may be provided continuously over a long period, rather than in spaced apart, higher doses, and the patches are easy to apply and use.

The patch must have an adhesive portion, to allow the patch to adhere to the skin. An adhesive suitable for use in a transdermal patch should possess certain properties, including adhesion, tack and cohesion. Adhesion refers to the force with which the adhesive sticks to a surface. Tack refers to the speed at which the adhesive can form a bond with the surface, while cohesion refers to the internal strength of an adhesive and its ability to resist splitting when placed under external stress. Good cohesion, in particular, is necessary for clean removal of the transdermal patch.

A primary use of the adhesive may be to affix a patch to the skin. However, it is preferable for the drug to be delivered to be incorporated into the adhesive, where possible, in order to reduce the amount of components and, therefore, expense necessary to make the patch.

A number of adhesives are already available for use in transdermal patches. Acrylic polymers are commonly used, as these possess adhesive properties which may easily be modulated by changing the composition of the polymer.

In connection with transdermal patches, US-A-5413776 discloses the use of a copolymer adhesive consisting of an acrylic acid ester polymer portion in combination with an N-vinyl-2 pyrrolidone polymeric portion. EP-A-450986 discloses the use of an alkyl methacrylate (co)polymer in combination with silicic acid anhydride, specifically for the delivery of nicotine. Both adhesives are acrylic copolymers.

EP-A-0450986 further discloses that a multi-functional monomer may be included as a copolymer, to provide chemical cross-links between the copolymer strands. Chemical cross-linking is thought to increase the degree of polymerisation and, thus, cohesion of the adhesive.

Block copolymers have also been used as adhesives for transdermal patches. A block copolymer consists of a mixture of 'hard' (A) and 'soft' (B) segments, which may be combined in an A-B-A or (A-B)_n type structure (*c.f.* Block Copolymers: Overview and Critical Survey, Noshay and McGrath, 1977). Association of the hard segments is thought to provide a degree of physical cross-linking, which improves the cohesive properties of the adhesive. One such example of a block copolymer adhesive is a polystyrene-polyisoprene-polystyrene (SIS) which is an A-B-A type block copolymer adhesive made by Shell, for example. This adhesive requires the use of an additional tackifier to provide suitable tack to the adhesive.

US 5,066,728 discloses a multiblock copolymer comprising endblocks of phenylbutadiene and an elastomeric midblock of a conjugated diene such as isoprene or butadiene. The copolymer is cross-linkable by electron beam radiation, such that the crosslinks are confined primarily to the end-block domains in the polymer, with minimal crosslinking occurring in the rubbery matrix. Blends of the copolymer with tackifier resins provide curable pressure sensitive adhesives.

JP-62036412A discloses vinyl chloride resins, produced by a graft copolymerisation of vinyl chloride and a block copolymer, wherein the copolymer contains a soft segment that

is crosslinked. The resins reportedly have a excellent impact resistance, weather-proofing properties and bending elasticity.

WO-97/01589 also discloses graft copolymers, suitable for use in influencing optical quality, dyeability, stability to weather or impact cracking and stress cracking in moulding compositions. The graft copolymers comprise a soft segment with at least one acrylate monomer, and a hard segment comprising at least one vinyl aromatic monomer. The soft segment is cross-linked, and the hard and soft segments are overlaid.

While a number of adhesives are available for use in transdermal patches, there is still a need for transdermal patch adhesives which possess excellent tack, cohesion and improved drug storage capacity.

It has now, surprisingly, been found that a degree of chemical cross-linking between the soft segments of a block copolymer can cause the copolymer to have enhanced properties, particularly with regard to cohesion and drug storage properties.

Thus, in a first aspect, the present invention provides a cross-linked block copolymer having drug retention properties, the block copolymer having hard and soft segments, characterised in that there is cross-linking between the soft segments.

Preferably, the block copolymer is an acrylic block copolymer. It is also preferred that the block copolymer is capable of acting as an adhesive, preferably on its own, but also in conjunction with one or more substances, such as those typically used in the manufacture of transdermal patches.

Thus, in a preferred aspect, there is provided a block copolymer, preferably an acrylic block copolymer, comprising soft and hard segments, that is suitable for use as an adhesive, characterised in that there is a degree of chemical cross-linking between the soft segments.

It will be appreciated that the term 'drug', as used herein, refers to any substance or compound suitable for administration *via* a transdermal patch. A substance having drug retention properties is taken herein as being a substance capable of absorbing or adsorbing a drug. In the instance where the substance is loaded with drug for dispensing *via* a transdermal patch, then it will be appreciated that such absorbance and/or adsorbance should be at least partially reversible.

The block copolymers of the present invention are simple to manufacture in an economic fashion, and may be selected for their drug retention and/or adhesive/cohesive properties. Accordingly, it is possible to provide an adhesive for use with a transdermal patch which allows the delivery of a greater amount of drug than is currently possible using known adhesives, as well as providing cleaner removal of used patches.

The term 'block copolymer', as used herein, refers to a macromolecule comprised of two, or more, chemically dissimilar polymer structures, terminally connected together (Block Copolymers: Overview and Critical Survey, Noshay and McGrath, 1977). These dissimilar polymer structures, sections or segments, represent the 'blocks' of the block copolymer. The blocks may generally be arranged in an A-B structure, an A-B-A structure, or a multiblock - (A-B)_n-system, wherein A and B are the chemically distinct polymer segments of the block copolymer.

It is generally preferred that the block copolymer of the present invention is of an A-B-A structure, especially wherein one of A and B is an acrylic type polymeric unit. It will be appreciated that the present invention is also applicable to block copolymers which possess three, or more different 'blocks', such as an A-B-C block copolymer. However, for convenience, reference hereinafter to block copolymers will assume that there are only A and B sub-units, but it will be appreciated that such reference also encompasses block copolymers having more than two different sub-units, unless otherwise specified.

It will be appreciated that the properties of block copolymers are very largely determined by the nature of the A and B blocks. Block copolymers commonly possess both

'hard' and 'soft' segments. A 'hard' segment is a polymer that has a glass transition temperature (T_g) and/or a melting temperature (T_M) that is above room temperature, while a soft segment is a polymer that has a T_g (and possibly a T_M) below room temperature. The different segments are thought to impart different properties to the block copolymer. Without being constrained by theory, it is thought that association of the hard segments of separate block copolymer units result in physical cross-links within the block copolymer, thereby promoting cohesive properties of the block copolymer. It is particularly preferred that the hard segments of the block copolymers of the present invention form such physical close associations.

The present invention preferably relates to acrylic block copolymers. In acrylic block copolymers, at least one of the blocks of the block copolymer is an acrylic acid polymer, or a polymer of an acrylic acid derivative. The polymer may be composed of just one repeated monomer species. However, it will be appreciated that a mixture of monomeric species may be used to form each of the blocks, so that a block may, in itself, be a copolymer. The use of a combination of different monomers can affect various properties of the resulting block copolymer. In particular, variation in the ratio or nature of the monomers used allows properties such as adhesion, tack and cohesion to be modulated, so that it is generally advantageous for the soft segments of the block copolymer to be composed of more than one monomer species.

It is preferred that alkyl acrylates and alkyl methacrylates are polymerised to form the soft portion of the block copolymer. Alkyl acrylates and alkyl methacrylates are thought to provide properties of tack and adhesion. Suitable alkyl acrylates and alkyl methacrylates include n-butyl acrylate, n-butyl methacrylate, hexyl acrylate, 2-ethylbutyl acrylate, isooctyl acrylate, 2-ethylhexyl acrylate, 2-ethylhexyl methacrylate, decyl acrylate, decyl methacrylate, dodecyl acrylate, dodecyl methacrylate, tridecyl acrylate and tridecyl methacrylate, although other suitable acrylates and methacrylates will be readily apparent to those skilled in the art. It is preferred that the acrylic block copolymer comprises at least 50% by weight of alkyl acrylate or alkyl methacrylate (co) polymer.

A polar monomer is advantageously copolymerised with the alkyl acrylate or alkyl methacrylate where it is desired to enhance the drug solubility of certain, especially hydrophilic, drugs. Suitable polar monomers which can be copolymerised with alkyl acrylates or alkyl methacrylates include hydroxyethyl acrylate, hydroxypropyl acrylate, vinyl pyrrolidone, acrylamide, dimethylacrylamide, acrylonitrile, diacetone acrylamide and vinyl acetate, although others will be apparent to those skilled in the art.

Diacetone acrylamide, or a combination of diacetone acrylamide and vinyl acetate, is useful in the present invention. The diacetone acrylamide component enables more advantageous drug loading capabilities than vinyl acetate, but vinyl acetate enhances the rate of polymerisation, which is of commercial importance. In such a case, where two polar monomers are used in an adhesive, it will be appreciated that the levels of each monomer may be manipulated in such a way as to provide optimum drug retention and delivery.

As stated above, variation in the components of the soft segment affects the overall properties of the block copolymer, although the essential feature remains the cross-linking of the soft segments. For example, soft segments essentially consisting of diacetone acrylamide with either butyl acrylate and/or 2-ethylhexyl acrylate, in approximately equal proportions, work well, and a ratio by weight of about 3 : 4 : 4 provides good results. It is preferred that diacetone acrylamide, or other polar monomer, such as hydroxyethyl methacrylate or vinyl acetate, be present in no more than 50% w/w of the monomeric mix of the soft segment, as this can lead to reduced adhesion, for example. However, where adhesion is not important, good levels of drug loading may be obtained with an excess of polar monomer. The acrylate component may generally be varied more freely, with good results observed with both 2-ethylhexyl acrylate and butyl acrylate together or individually, although with greater hydrophobic side chain size, there is a slight decrease in drug loading, both for hydrophobic and hydrophilic drugs.

As noted above, ratios of the various monomers are generally preferred to be approximately equal. For adhesives, this is preferred to be with a polar component of 50% or less of the soft segment, with the apolar portion forming up to about 85% w/w, but preferably

between about 50 and 70% w/w. In the example above, this is about 72% (4+4) apolar to about 18% (3) polar.

In general, it is preferred that the combination of monomers chosen produces an adhesive, and that the adhesive has a combination of good drug loading, cohesion and adhesion, such that it is suitable for use with a transdermal patch. When varying the monomers and their different ratios, it is preferred to retain good drug loading properties.

Prior art adhesives are generally capable of drug loading of up to about 5% w/w adhesive. Block copolymers of the present invention, depending on composition, can often load in excess of 15%, but loading of between 5 and 10% is readily obtainable. Drug loading of less than 5% is occasionally observed, depending on the constitution and method of preparation of the block copolymer, but this is acceptable, especially where other properties, such as cohesion, are important.

It will be appreciated that compounds with high drug retention properties but reduced adhesion may also be suitable as an adhesive for use with a medical patch. Such adhesives may be appropriate for use in a transdermal patch which need only be applied for a short time or, alternatively, the adhesive may be used in combination with a further agent, such as an enhancer, for example polyethylene glycol, Azone (Trade Mark), vitamin E or liquid paraffin, to increase its adhesive properties.

As discussed above, polymers suitable for use as the hard portion of the block copolymer possess glass transition temperatures above room temperature. Suitable monomers for use in forming the hard segment polymer include styrene, α -methylstyrene, methyl methacrylate and vinyl pyrrolidone, although other suitable monomers will be readily apparent to those skilled in the art. Styrene and polymethyl methacrylate have been found to be suitable for use in the formation of the hard segment of the block copolymers of the present invention.

It is preferred that the hard portion of the block copolymer forms from 3-30% w/w of the total block copolymer, particularly preferably from 5-15% w/w.

The block copolymer of the present invention is characterised in that the soft portions contain a degree of chemical cross-linking. Such cross-linking may be effected by any suitable cross-linking agent. It is particularly preferable that the cross-linking agent be in the form of a monomer suitable for incorporation into the soft segment during polymerisation. Preferably the cross-linking agent has two, or more, radically polymerisable groups, such as a vinyl group, per molecule of the monomer, at least one tending to remain unchanged during the initial polymerisation, thereby to permit cross-linking of the resulting block copolymer.

Suitable cross-linking agents for use in the present invention include divinylbenzene, methylene bis-acrylamide, ethylene glycol di(meth)acrylate, ethylene glycol tetra(meth)acrylate, propylene glycol di(meth)acrylate, butylene glycol di(meth)acrylate, or trimethylolpropane tri(meth)acrylate, although other suitable cross-linking agents will be readily apparent to those skilled in the art. A preferred cross-linking agent is tetraethylene glycol dimethacrylate. It is preferred that the cross-linking agent comprises about 0.01-0.6% by weight of the block copolymer, with 0.1-0.4% by weight being particularly preferred.

Methods for the production of block copolymers from their monomeric constituents are well known. The block copolymer portions of the present invention may be produced by any suitable method, such as step growth, anionic, cationic and free radical methods (Block Copolymers, *supra*). Free radical methods are generally preferred over other methods, such as anionic polymerisation, as the solvent and the monomer do not have to be purified.

Suitable initiators for polymerisation include polymeric peroxides with more than one peroxide moiety per molecule. One suitable initiator has been found to be 'Perhexa MC' (1,1'-di-*tert*butyl-peroxy-2-methyl cyclohexane, Nihon Yusi C.C.). This compound contains two tertiary butyl peroxy groups which allow stepwise polymerisation of the hard and soft segments of the block copolymer. The initiator CH-50-AL (Peroxid-Chemie GmbH) has also been found to be suitable in the manufacture of compounds of the present invention. Choice

of reaction conditions is well within the skill of one in the art, once a suitable initiator has been chosen.

The initiator is preferably used in an amount of 0.005-0.1% by weight of the block copolymer, with 0.01-0.05% by weight being particularly preferred, although it will be appreciated that the amount chosen is, again, well within the skill of one in the art. In particular, it is preferred that the amount should not be so much as to cause instant gelling of the mix, nor so low as to slow down polymerisation and to leave excess residual monomers. A preferred level of residual monomers is below 2000 ppm. It will also be appreciated that the amount of initiator will vary substantially, depending on such considerations as the initiator itself and the nature of the monomers.

The block copolymers of the present invention are preferably adhesives, particularly preferably pressure sensitive adhesives. Pressure sensitive adhesives can be applied to a surface by hand pressure and require no activation by heat, water or solvent. As such, they are particularly suitable for use with transdermal patches. Block copolymer adhesives of the present invention are particularly suitable for use in combination with a transdermal patch.

A number of adhesives currently used in transdermal patches require the use of a tackifier, to provide improved tack. The block copolymers of the present invention are suitable for use without a tackifier and, as such, are particularly advantageous. However, it will be appreciated that the block copolymers of the present invention are also suitable for use in combination with a tackifier, should one be required or desired. Suitable tackifiers are well known and will be readily apparent to those skilled in the art.

Without being constrained by theory, it is thought that the combination of chemical cross-links between the soft segments of the copolymer combined with the, generally, hydrophobic interaction, or physical cross-linking, between the hard portions results in a 'matrix-like' structure. Copolymers having only physical cross-linking of the hard segments are less able to form such a matrix. It is believed that the combination of both forms of cross-

linking of the block copolymers of the present invention provides both the increased internal strength (cohesion) and also the significantly improved drug storage capacity that is observed.

Essentially, it is believed that the hard segments associate to form islands, or nodes, with the soft segments radiating from and between these nodes. Where the soft segment is the B segment of an ABA structure, then it needs to be as long as possible to permit ingress of drug.

In the block copolymers of the present invention, there is a defined physical structure in the 'sea' between the islands, where the soft segments are cross-linked, so that there is no necessity for extensive intermingling of the soft segments. This results in a greater cohesion of the whole block copolymer while, at the same time, allowing shortened soft segment length and still having as great, or greater, distances between the islands. This permits greater drug storage capacity. Even where soft segment length is reduced to 50% or lower than that of the art, the adhesives still have a greater cohesion and can also be manufactured more easily (*infra*).

It is thought that the ability of a copolymer adhesive to retain a drug is related to the length of the copolymer chains and the degree of cross-linking. The improved drug storage capacity of the block copolymer of the present invention allows reduction in the length of polymer chains in comparison to other copolymers that are used as adhesives, while still providing improved drug storage. Further, shortening of the polymer chains reduces the viscosity of the block copolymer, which is particularly advantageous in the manufacture of the adhesive.

Thus, there is further provided a transdermal patch comprising a block copolymer of the present invention, the block copolymer preferably being an adhesive.

The term 'transdermal patch', as used herein, is used to describe any means which may be applied to the skin and which may be used to deliver a drug or pharmaceutical preparation onto, and preferably through, the skin layer, typically the dermis. Transdermal

patches generally comprise a drug-impermeable backing portion and an adhesive. The adhesive serves to stick the patch onto the skin and may also serve to contain and deliver the drug. The transdermal patch may be any patch that is suitable for use in combination with the block copolymer adhesive of the present invention.

It will be appreciated that the enhanced drug storage capacity of the block copolymer of the present invention allows improvements to be made in the design of transdermal patches. For example, patches which are smaller than those currently available can be made and which may still supply a therapeutically effective amount of a drug owing to the greater drug storage capacity and delivery of the block copolymers of the present invention.

The block copolymer of the present invention also allows for more straightforward manufacturing of transdermal patches. Acrylic adhesives which may be used in transdermal patches are commonly cross-linked to harden them by the use of isocyanates. However, isocyanate cross-linking must be carried out just prior to coating of a transdermal patch, because the cross-linking reaction begins immediately. If the adhesive is left to cross-link for too long, then it can no longer be coated onto the patch. However, the block copolymer of the present invention cross-links as the solvent is removed, so that cross-linking can be timed to occur after coating, this being the preferred method. Accordingly, not only can the block copolymer easily be applied to the patch, but the complete solution can also be stored for a period before coating.

Accordingly, there is also provided a process for the manufacture of a cross-linked block copolymer having drug retention properties, the block copolymer having hard and soft segments, there being cross-linking between the soft segments, the process comprising polymerising the monomeric constituents of each soft segment in solution, then adding the constituents of the hard segment to each resulting solution and polymerising the resulting mix, followed by cross-linking by removal of any solvent.

There is also provided such a complete solution, which provides cross-linked block copolymer of the present invention on removal of the solvent or solvent system, such as by

evaporation. If the solution is to be stored for any length of time, it may be necessary to keep the polymer from precipitating out, and this may be achieved by known means, such as by suspending agents or shaking. It may also be necessary to select the type of polymers that will be subject to substantially no cross-linking until the solvent is evaporated.

Suitable examples of drug-impermeable backings which may be used for transdermal patches include films or sheets of polyolefins, polyesters, polyurethanes, polyvinyl alcohols, polyvinyl chlorides, polyvinylidene chloride, polyamides, ethylene-vinyl acetate copolymer (EVA), ethylene-ethylacrylate copolymer (EEA), vinyl acetate-vinyl chloride copolymer, cellulose acetate, ethyl cellulose, metal vapour deposited films or sheets thereof, rubber sheets or films, expanded synthetic resin sheets or films, non-woven fabrics, fabrics, knitted fabrics, paper and foils. Other backings will be readily apparent to those skilled in the art.

Suitable drugs are typically biologically active compounds or mixture of compounds that have a therapeutic, prophylactic or other beneficial pharmacological or physiological effect. Examples of drugs that may be used in combination with the block copolymer of the present invention include anti-arrhythmic drugs, anticoagulants, antidiabetics, antiepileptics, antifungals, antigout, antimalarials, antimuscarinic agents, antineoplastic agents, antiprotozoal agents, thyroid and antithyroid agents, anxiolytic sedatives and neuroleptics, beta blocking agents, drugs affecting bone metabolism, cardiac inotropic agents, chelating agents, antidotes and antagonists, corticosteroids, cough suppressants, expectorants and mucolytics, dermatological agents, diuretics, gastro-intestinal agents, general and local anaesthetics, histamine H1 receptor antagonists, nitrates, vitamins, opioid analgesics, parasympathomimetics, anti-asthma agents, muscle relaxants, stimulants and anorectics, sympathomimetics, thyroid agents, xanthines, lipid regulating agents, antiinflammatory drugs, analgesics, antiarthritic drugs, antispasmodics, antidepressants, antipsychotic drugs, tranquillisers, narcotic antagonists, antiparkinsonism agents, cholinergic agonists, anticancer drugs, immunosuppressive agents, antiviral agents, antibiotic agents, appetite suppressants, antiemetics, anticholinergics, antihistamines, antimigraine agents, coronary, cerebral or peripheral vasodilators, hormonal agents, contraceptive agents, antithrombotic agents,

diuretics, antihypertensive agents and cardiovascular drugs. Other drugs will be readily apparent to those skilled in the art.

Examples of specific drugs include steroids such as oestradiol, levonorgestrel, norethisterone, testosterone and their esters; nitro-compounds such as nitroglycerine and isosorbide nitrates; nicotine, scopolamine; oxycam derivatives such as lornoxicam, ketoprofen, fentanyl, salbutamol, terbutaline, selegiline and clonidine, as well as pharmaceutically acceptable equivalents thereof and pharmaceutically acceptable esters and the salts of such compounds with pharmaceutically acceptable acids and bases as appropriate.

It will be appreciated that the above classes of drug, or specific drugs, are individually contemplated for use with a transdermal patch of the present invention.

It will be appreciated that, while various drugs have been exemplified above, some drugs are more suitable for use in transdermal delivery systems than others. While a transdermal delivery system may deliver a quantity of a drug, this quantity may not be the optimum therapeutic dose. Essentially, any drug that can be delivered by a patch and which does not substantially crystallise at levels too low to be useful is envisaged as being useful in patches of the present invention.

It will be appreciated that the present invention also envisages the use of permeation enhancers which allow greater permeation of the drug into the skin. Compounds suitable for use as permeation agents include compounds containing at least one amide bond, esters of lactic acid, lactic acid, salts of lactic acid, dicarboxylic acids, salts of dicarboxylic acids, citric acid and salts of citric acid, O-alkyl (polyoxyethyl)phosphates and esters of higher fatty acids, carboxylic acids of glycerin and ethers of polyoxyethylene and monoalcohols. Suitable enhancers include lauryl di-methanol amide, glycerin monolaurate, glycerin triacetate and polyoxyethylene lauryl ether.

Other specific examples of permeation enhancers include PEG (polyethylene glycol), liquid paraffin, Azone and vitamin E. In addition, such enhancers may improve the adhesive

qualities of the block copolymer of the invention and, where used, it may be desirable to select an adhesive with lower adhesive properties. Alternatively, such enhancers may be used to supplement a block copolymer have low adhesive qualities.

The present invention also envisages the use of suitable agents to inhibit crystallisation of the drug in the adhesive. Many agents will be apparent to those skilled in the art, and polyethylene glycol is generally particularly effective. However, it has been found that a further advantage of the adhesives of the present invention is that compounds to be delivered are generally less likely to crystallise than they are in prior art systems.

The present invention will now be illustrated further with reference to the following, non-binding Examples.

Example 1

Drug saturation

The ability of the block copolymer of the present invention to store drugs was compared with a polystyrene-polyisoprene-polystyrene based adhesive (hereinafter termed 'SIS') used in transdermal patches (KrantonD-1101TM, Shell Chemicals).

For the purpose of the comparative studies, the SIS block copolymer was mixed with tackifier (Arkon P-100, Arakawa Chemicals, Osaka, Japan) and paraffin in the ratio 1 : 1.6 : 1.2 by weight respectively. This mixture provides optimised adhesive properties.

Three drugs, isosorbide mononitrate (ISMN), indomethacin and ketoprofen, were used in the present Example. Each of the drugs was mixed with each of the two adhesives, such that a range of concentrations of drug were obtained in each adhesive. Each adhesive/drug mix was then applied to a backing film, and the film allowed to dry. After drying, the films were assessed for drug crystallisation.

More specifically, the compound of the present invention was dissolved in ethyl acetate to form 39% by weight of the final solution. The SIS adhesive was dissolved in chloroform, to a final concentration of 19% by weight of the final solution. Each drug was dissolved in methanol to a final concentration of 5% by weight.

The adhesives and drug solutions were mixed together in suitable proportions such that a range of different drug concentrations were produced. The mix was then applied to a polyethylene terephthalate (herein abbreviated to 'PET') film. The solvents were evaporated off at 60°C, such that thin films of adhesive containing the drug were left. All the films were then left at 50° C for 48 hours, then room temperature for 48 hours. Crystal formation was assessed.

The following range of drug concentrations was chosen:

SIS adhesive: 1%, 2%, 3%, 5%, 7.5%, 10% (w/w adhesive)

Adhesive of the invention: 10%, 12.5%, 15%, 17.5%, 20% (w/w adhesive)

It was not possible to obtain concentrations of drug above 10% in the SIS adhesive. The saturation concentration of each drug was determined, which was defined as the maximum concentration of drug at which no crystal formation was observed. The results of the experiment are shown in Table 1 below.

Table 1

Drug	Saturation concentration (%w/w adhesive)	
	Adhesive of the invention	SIS
ISMN	>20%	5%
Ketoprofen	17.5%	1
Indomethacin	15	<1%

It can be seen from the above Table that drug crystallised in the SIS adhesive at very substantially lower concentrations than in the compound of the invention, both ketoprofen and indomethacin being essentially unusable in SIS. Thus, the compound of the present invention is able to incorporate greater quantities of drug than SIS adhesive before crystal formation occurs.

Example 2

Drug delivery

The ability of an adhesive compound of the present invention to release ISMN was compared to that of the SIS adhesive.

Transdermal patches were manufactured, each containing each of the adhesives in combination with ISMN. The test patches were applied to two volunteers for 24 hours. After this time, the test patches were removed, and the residual drug levels were measured. The quantity of ISMN in a standard (control) patch was measured, to obtain a reference value. Comparison of the residual drug content of the test patches with the total drug content of the control patch allows the total amount of drug release from the patch to be determined.

More specifically, a 20% w/w solution of ISMN in methanol was prepared. The ISMN solution was mixed with a quantity of either the SIS adhesive or the adhesive of the present invention, sufficient to obtain the desired final drug concentration. Each adhesive-drug mix was coated onto a 30 μm PET film (release liner). Thus, after drying, the adhesive layer had been laminated onto a PET backing film. The films were then punched to form circular patches of 3cm diameter.

After having been used on the patients for 24 hours, patches containing the SIS adhesive were placed in 15 cm^3 of chloroform for 24 hours to dissolve the ISMN. Methanol

was then used to precipitate the ISMN from the chloroform solution. ISMN levels were then determined by High Pressure Liquid Chromatography (HPLC).

Patches containing the adhesive of the present invention were placed directly in 30cm³ of methanol for 24 hours, in order to dissolve the remaining ISMN. The concentration of ISMN was determined by HPLC as above.

In this latter case, methanol alone is sufficient to release drug from the adhesive of the present invention, and a chloroform step is not required. For comparative purposes, it has been shown that a chloroform-methanol extraction of ISMN from the adhesive of the present invention produces identical results to that of a simple methanol extraction. Thus, the results below are directly comparable and are not affected by the different extraction techniques used.

Drug release from the following patches was assessed, and the results are shown in Table 2 below.

Table 2

Adhesive	ISMN Concentration (% w/w of the adhesive)
Adhesive of present invention	10% and 20%
SIS adhesive	3% and 5%

It was not possible to provide more than 5% w/w of ISMN in the SIS adhesive. Therefore, the relative drug release from the different adhesives is not directly comparable. However, it is the absolute amount of drug release that is important in this case. Table 3 below shows the effective maximum levels of drug release to the volunteer for each adhesive.

Table 3

	Adhesive			
	Adhesive of the present invention (10% ISMN)	Adhesive of the present invention (20% ISMN)	SIS (3% ISMN)	SIS (5% ISMN)
Drug content (mg)				
Control patch	6.5	9.8	1.9	3.83

Residual drug content (mg)				
Volunteer A	4.6	7.4	1.54	2.38
Volunteer B	5.1	8.1	1.88	3.48

Total drug release (mg)				
Volunteer A	1.9	2.4	0.46	1.45
Volunteer B	1.4	1.7	0.02	0.35

From the above table, it can be seen that the total drug that may be released from the patch is much greater when the adhesive of the present invention is used. This is related to the ability of the adhesive of the present invention to contain a greater initial quantity of drug. Further, drug release continues from the patches of the invention after the test period of 24 hours.

Example 3

Preparation of Adhesive Compounds of the Present Invention

The adhesive compound used in Examples 1 and 2 was made in a two step synthesis:

Step 1:

115g of 2-ethylhexyl acrylate, 84g of diacetone acrylamide, 115g of butyl acrylate and 0.72g tetraethylene glycol dimethacrylate were mixed, in order to obtain a homogeneous solution. The solution was placed in a flask, and 200 cm³ of ethyl acetate along with 200 cm³ of toluene were added. The solution was heated to 80°C under nitrogen, then 0.05 g of 1,1'-di-*tert*-butylperoxy-2-methyl cyclohexane dissolved in 10 cm³ of ethyl acetate were added. Polymerisation was allowed to proceed for 24 hours. This step produced the soft segments.

Step 2:

After 24 hours, 45g methyl methacrylate and 300 cm³ of toluene were added to the mix of Step 1. The solution was then heated to 99°C in order to initiate the second stage polymerisation step, which was continued for 12 hours.

After this time, the polymer was transferred to a bottle for cooling. The resulting solution represented a pre-crosslinked polymer, used in subsequent experiments. The average molecular weight of the polymer produced in this way was estimated to be 358,000 Da by gel permeation chromatography.

Example 4**Comparative Cohesion Studies**

There are no industry standard tests for measuring cohesion. Cohesive strength of the adhesives was assayed as follows.

The polymer solution of Example 3 was applied to a backing strip. Evaporation of the solvent resulted in a cross-linked adhesive compound. One end of the strip was then stuck to a glass plate, angled at 20° from the vertical. The rest of the strip was allowed to hang vertically. A weight was then suspended from the free end of the strip. The time taken for

the strip to detach from the plate (*i.e.* for the strip and weight to fall to the ground) was measured.

More specifically, in this Example, the SIS adhesive was compared with the adhesive compound of the present invention. The SIS adhesive contained 5%, by weight, of ISMN, while the adhesive of the present invention contained 10% by weight of ISMN.

Strips of length 5 cm and width 0.6 cm, coated with one of each of the adhesive-drug mixtures, were attached to a glass plate. The total adhesion area in each case was 0.36 cm². An 80g weight was used. The measurements were taken at 25°C.

The time taken for each strip to become detached from the plate is shown in Table 4 below.

Table 4

	Time taken to become detached	
	Adhesive of the invention	SIS adhesive
Sample Strip 1	> 30 minutes*	7.5 minutes
Sample Strip 2	> 30 minutes*	6.0 minutes

* Detached by 24 hours

It can be seen from the above table that the adhesive of the present invention takes significantly longer to become detached from the glass plate, in comparison with the SIS adhesive under the same conditions. Therefore, the adhesive of the present invention has significantly enhanced cohesive properties with respect to the SIS adhesive.

Example 5**Effects of Variation in Monomer Composition**

A number of variations of the adhesive of the invention were prepared, in order to determine the effect of variation in the composition.

5.1 Initial variants were tested for cohesion. The compositions tested are shown in Table 5 below.

Table 5

Component	Composition							
	A	B	C	D	E	F	X	Y
2-ethylhexyl acrylate (g)	115	115	115	115	115	115	258	258
Butyl acrylate (g)	115	115	115	115	115	115		
Diacetone acrylamide (g)	84	84	84	84	84	21	42	42
Ethyl acrylate (g)						63		
Tetraethylene glycol dimethacrylate (g)	0.72	0.72	0.36	0.48	1.5	0.48	0.24	0.48
Methyl methacrylate (g)	45	30	45	30	45	30	30	30
Cohesion (min's)	> 20	3-10	3-10	< 3	N/A ¹	N/A ¹	< 1	< 1

1 Data not available

In all the above cases, the solvents used were toluene (500 mls) and ethyl acetate (200mls). The initiator was Perhexa MC (0.05 mg) in all cases.

From the above, it can be seen that composition A represents an adhesive with excellent cohesion. The results obtained with B and C indicate some of the variations that can be made and a suitable composition still obtained.

Composition D contains comparatively low levels of both tetraethylene glycol dimethacrylate and methyl methacrylate. This adhesive has lowered cohesion compared with B or C, each of which have only of these two amounts reduced.

Compositions E and F produce gel-like polymers, which are not preferred as an adhesive suitable for use with a transdermal patch, while X and Y had low levels of each of diacetone acrylamide, tetraethylene glycol dimethacrylate and methyl methacrylate, and produced a sticky polymer with weak cohesion.

5.2 A number of further adhesives were made, with different compositions. These were tested for adhesion, cohesion and drug retention. These compositions and properties are presented in Table 6 below.

TABLE 6

		Composition									
		G	H	I	J	K	L	M	N	O	P
Monomer ¹											
2-Ethylhexyl acrylate		110	110			55	55		55	55	
Butyl acrylate				110	110	55	55	110	55	55	110
Hydroxyethyl methacrylate						75					
Diacetone acrylamide		110	55	75	75		75		75	75	100
Vinyl acetate									37.5	37.5	40
Tetraethylene glycol dimethacrylate		0.35	0.35	0.35	0.5	0.35	0.35	0.35	0.35	0.35	0.35
Methyl methacrylate		25	15	15	15	15	-	15	15	15	15
Styrene							15				
Initiator ¹											
Perhexa MC		0.09	0.14	0.14	0.14	0.14	0.14	0.14	0.14	0.21	0.14
Solvent ²											
Ethyl acetate		200	200	200	200	200	200	200	300	300	300
Toluene		250	250	250	250	250	250	250	350	350	350
Adhesive properties ³											
Adhesion		Slight	Good	Good	N/A ⁵	Slight	Good	Slight	Good	N/A ⁵	No adhesion
Cohesion		5	10	>15	N/A ⁵	10	>15	10	>15	N/A ⁵	0
Drug loading property ⁴											
Piroxicam		5	5	8	N/A ⁵	5	6	4	8	N/A ⁵	10
Oestradiol		8	8	15	N/A ⁵	6	10	<4	15	N/A ⁵	>15

1 units = grams

2 units = ml

3 units = minutes

4 units = grams per 100 g of adhesive

5 Not available

From the above, it can be seen that compositions G, H, I, K, L, M and N show good drug retention properties, in combination with suitable cohesive and adhesive properties. These adhesives are suitable for use in combination with transdermal patches.

Compounds J and O, which have high levels of tetraethylene glycol dimethacrylate and Perhexa MC, produced a product which gelled at the first stage of polymerisation. Such compounds are not suitable for use as adhesives for transdermal patches.

Compound P, with a high level of hydrophilic monomers, produced a product with no adhesion. This compound is unsuitable for use as an adhesive for transdermal patches, unless adhesion can be generated in the presence of an enhancer. In any event, this compound may be suitable for use with transdermal patches as a drug retention agent, even if an extra adhesive is necessary, owing to its great drug retention.

Comparative Example 1

Cohesion and Drug Loading Capacity of Commercially Available Adhesives

Two commercially available adhesives used in transdermal patches were tested for drug loading capacity, using the drugs piroxicam and oestradiol. The adhesives were National Starch 837-2516 and National Starch 387-2052.

Each drug showed cohesion of greater than 15 minutes.

National Starch 837-2516 was able to hold 4 g of piroxicam and 4g of oestradiol, per 100 g of adhesive.

National Starch 837-2052 was able to hold 4g of piroxicam and 2 g of oestradiol, per 100 g of adhesive.

Thus, by comparison with Table 6 above, the National Starch adhesives show equivalent drug loading properties to composition M, while all other compounds of Table 6 for which drug loading was tested showed improved drug loading with respect to the commercially available products.

Example 6

Use of Initiator CH-50-AL

Experiments were carried out using the initiator CH-50-AL, in place of Perhexa MC. CH-50-AL is 1,1-di(*tert*-butylperoxy)cyclohexane, and is available from Peroxid-Chemie GmbH. The compositions listed in Table 7 below were tested.

Table 7

	Composition	
	Q	R
Monomer¹		
2-Ethylhexyl acrylate	85	85
Butyl acrylate	85	85
Diacetone acrylamide	63	63
Tetraethylene glycol dimethacrylate	0.25	0.25
Methyl methacrylate	20	20
Initiator¹		
CH-50-AL	0.1	0.1
Solvent²		
First stage		
Ethyl acetate	150	150
Toluene	150	50
Second stage		
Toluene	150	150
Temperature		
first stage	90	90
second stage	98	98
Cohesive properties		
Cohesion	5 minutes	> 20 minutes

1 units = grams

2 units = mls.

Claims

1. A cross-linked block copolymer having drug retention properties, the block copolymer having hard and soft segments, characterised in that there is cross-linking between the soft segments.
2. A block copolymer, according to claim 1, which is an acrylic block copolymer.
3. A block copolymer, according to claim 1 or 2, wherein the block copolymer is an adhesive.
4. A block copolymer, according to claim 3, wherein the block copolymer is an adhesive when in conjunction with one or more enhancers.
5. A block copolymer according to any preceding claim, which has an A-B-A structure.
6. A block copolymer according to claim 5, wherein one of A and B is an acrylic type polymeric unit.
7. A block copolymer according to any preceding claim, wherein the soft portion of the block copolymer comprises monomeric units selected from alkyl acrylates and alkyl methacrylates.
8. A block copolymer according to claim 7, wherein the monomeric units are selected from n-butyl acrylate, n-butyl methacrylate, hexyl acrylate, 2-ethylbutyl acrylate, isooctyl acrylate, 2-ethylhexyl acrylate, 2-ethylhexyl methacrylate, decyl acrylate, decyl methacrylate, dodecyl acrylate, dodecyl methacrylate, tridecyl acrylate and tridecyl methacrylate and mixtures thereof.
9. A block copolymer according to claim 7 or 8, wherein the acrylic block copolymer comprises at least 50% by weight of alkyl acrylate or alkyl methacrylate (co) polymer.

10. A block copolymer according to any of claims 7 to 9, wherein a polar monomer is copolymerised with the alkyl acrylate or alkyl methacrylate.
11. A block copolymer according to claim 10, wherein said polar monomer is selected from hydroxyethyl acrylate, hydroxypropyl acrylate, vinyl pyrrolidone, acrylamide, dimethylacrylamide, acrylonitrile, diacetone acrylamide, vinyl acetate and mixtures thereof.
12. A block copolymer according to any preceding claim, wherein diacetone acrylamide is an ingredient of at least one soft portion.
13. A block copolymer according to any preceding claim, which is an adhesive, wherein the adhesive properties are enhanced by a further agent.
14. A block copolymer according to claim 13, wherein the enhancer is polyethylene glycol, Azone, vitamin E or liquid paraffin.
15. A block copolymer according to claim 13, wherein the enhancer is lauryl di-methanol amide, glycerin monolaurate, glycerin triacetate or polyoxyethylene lauryl ether.
16. A block copolymer according to any preceding claim, wherein the hard segment polymer is formed from styrene, α -methylstyrene, methyl methacrylate, vinyl pyrrolidone or a mixture thereof.
17. A block copolymer according to claim 16, wherein the hard segment polymer is formed from styrene and/or polymethyl methacrylate.
18. A block copolymer according to any preceding claim, wherein the hard portion of the block copolymer forms from 3-30% w/w of the total block copolymer.

19. A block copolymer according to claim 18, wherein the hard portion of the block copolymer forms from 5-15% w/w of the total block copolymer.
20. A block copolymer according to any preceding claim, which is a pressure sensitive adhesive.
21. A transdermal patch comprising a block copolymer according to any preceding claim.
22. A patch according to claim 21, loaded with a drug selected from anti-arrhythmic drugs, anticoagulants, antidiabetics, antiepileptics, antifungals, antigout, antimalarials, antimuscarinic agents, antineoplastic agents, antiprotozoal agents, thyroid and antithyroid agents, anxiolytic sedatives and neuroleptics, beta blocking agents, drugs affecting bone metabolism, cardiac inotropic agents, chelating agents, antidotes and antagonists, corticosteroids, cough suppressants, expectorants and mucolytics, dermatological agents, diuretics, gastro-intestinal agents, general and local anaesthetics, histamine H1 receptor antagonists, nitrates, vitamins, opioid analgesics, parasympathomimetics, anti-asthma agents, muscle relaxants, stimulants and anorectics, sympathomimetics, thyroid agents, xanthines, lipid regulating agents, antiinflammatory drugs, analgesics, antiarthritic drugs, antispasmodics, antidepressants, antipsychotic drugs, tranquillisers, narcotic antagonists, antiparkinsonism agents, cholinergic agonists, anticancer drugs, immunosuppressive agents, antiviral agents, antibiotic agents, appetite suppressants, antiemetics, anticholinergics, antihistamines, antimigraine agents, coronary, cerebral or peripheral vasodilators, hormonal agents, contraceptive agents, antithrombotic agents, diuretics, antihypertensive agents and cardiovascular agents.
23. A patch according to claim 22, wherein the drug is a steroid, or a salt or ester thereof.
24. A patch according to claim 23, wherein the drug is oestradiol, levonorgestrel, norethisterone, testosterone or a salt or ester thereof.

25. A patch according to claim 22, wherein the drug is a nitro-compound or a salt or ester thereof.
26. A patch according to claim 25, wherein the drug is nitroglycerine or an isosorbide nitrate or a salt or ester thereof.
27. A patch according to claim 25, wherein the drug is nicotine or scopolamine or a salt or ester thereof.
28. A patch according to claim 22, wherein the drug is an oxicam derivative or a salt or ester thereof.
29. A patch according to claim 28, wherein the drug is lornoxicam, ketoprofen, fentanyl, salbutamol, terbutaline, selegiline or clonidine or a salt or ester thereof.
30. A process for the manufacture of a cross-linked block copolymer having drug retention properties, the block copolymer having hard and soft segments, there being cross-linking between the soft segments, the process comprising polymerising the monomeric constituents of each soft segment in solution, said constituents including at least one cross-linking agent, then adding the constituents of the hard segment to each resulting solution and polymerising the resulting mix, followed by cross-linking by removal of any solvent, an initiator being added before adding the constituents of the hard segment.
31. A process according to claim 30, wherein the block copolymer is so produced as to have the properties of a block copolymer according to any of claims 1 to 20.
32. A process according to claim 30 or 31, wherein the cross-linking agent is in the form of at least one monomer suitable for incorporation into the soft segment during polymerisation.

33. A process according to claim 32, wherein the at least one cross-linking agent has two, or more, radically polymerisable groups.
34. A process according to claim 32 or 33, wherein the at least one cross-linking agent is selected from divinyl- benzene, methylene bis-acrylamide, ethylene glycol di(meth)acrylate, ethylene glycol tetra(meth)acrylate, propylene glycol di(meth)acrylate, butylene glycol di(meth)acrylate, and trimethylolpropane tri(meth)acrylate.
35. A process according to any of claims 32 to 34, wherein the at least one cross-linking agent is tetraethylene glycol dimethacrylate.
36. A process according to any of claims 32 to 35, wherein the cross-linking agent comprises 0.01-0.6% by weight of the block copolymer.
37. A process according to claim 32, wherein the cross-linking agent comprises 0.1-0.4% by weight of the block copolymer.
38. A process according to any of claims 30 to 37, wherein the initiator is 1,1'-di-*tert*-butylperoxy-2-methylcyclohexane.
39. A process according to any of claims 30 to 38, wherein the initiator is used in an amount of 0.005-0.1% by weight of the block copolymer.
40. A process according to claim 39, wherein the initiator is used in an amount of 0.01-0.05% by weight.
41. A process according to any of claims 30 to 40, wherein a polar monomer comprises up to 50% w/w of the monomers of any soft segment.
42. A process according to claim 41, wherein a polar monomer comprises in excess of 15% w/w of the monomers of any soft segment.

INTERNATIONAL SEARCH REPORT

Inter national Application No
PCT/GB 98/02018

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 A61K9/70 C08F265/06 C08L51/00 C08L53/00 C09J151/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 C08F C08L A61K C09J		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 443 864 A (MITSUBISHI PETROCHEMICAL CO) 28 August 1991 see page 5, line 19 - page 6, line 30 see page 4, line 19-50 ---	1,2, 5-10, 16-19
X	GB 2 056 999 A (NITTO ELECTRIC IND CO) 25 March 1981 see the whole document ---	1-20
A	US 4 575 539 A (DECROSTA MARK T ET AL) 11 March 1986 see the whole document ---	1-42
A	US 5 573 778 A (RODGERS KENNETH W ET AL) 12 November 1996 see claims 1,9A ---	1-42
-/--		
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
* Special categories of cited documents : <div style="display: flex;"> <div style="flex: 1;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"Z" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">30 September 1998</div>	Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">12/10/1998</div>	
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3018	Authorized officer <div style="text-align: center; font-weight: bold;">Meulemans, R</div>	

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 98/02018

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 186 938 A (SABLITSKY STEVEN ET AL) 16 February 1993 see the whole document -----	21
A	US 5 082 663 A (KONISHI RYOJI ET AL) 21 January 1992 see the whole document -----	1-42

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/02018

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0443864 A	28-08-1991	JP 3244609 A	31-10-1991
		JP 3244610 A	31-10-1991
		JP 4001217 A	06-01-1992
		US 5183856 A	02-02-1993
GB 2056999 A	25-03-1981	NONE	
US 4575539 A	11-03-1986	NONE	
US 5573778 A	12-11-1996	AU 4808596 A	26-09-1996
		CA 2171911 A	18-09-1996
		EP 0732100 A	18-09-1996
		JP 8319464 A	03-12-1996
US 5186938 A	16-02-1993	AU 576889 B	08-09-1988
		AU 4676185 A	25-02-1986
		EP 0190262 A	13-08-1986
		FI 861177 A,B	20-03-1986
		HK 94093 A	17-09-1993
		JP 4040326 B	02-07-1992
		JP 61502760 T	27-11-1986
		WO 8600814 A	13-02-1986
US 5082663 A	21-01-1992	JP 63051330 A	04-03-1988
		JP 63051333 A	04-03-1988
		HK 77194 A	12-08-1994
		KR 9513750 B	15-11-1995
		DE 3775208 A	23-01-1992
		EP 0280737 A	07-09-1988
		WO 8801170 A	25-02-1988
		SG 29994 G	10-06-1994